

In the Specification

Please add following paragraph as the first paragraph on page 1 of the specification, following the title and before TECHNICAL FIELD.

Page 1, paragraph 1 (New)

This application is the National Stage of International Application No. PCT/JP00/05524, filed August 18, 2000.

Please substitute the following paragraph for the second paragraph starting on page 5 of the specification.

Page 5, paragraph 2 (Currently Amended)

Lipid peroxidation inhibitory agents (antioxidants), which have lipid peroxidation inhibitory activity based on excellent antioxidant activity and are excellent in pharmacokinetics, can be expected to have excellent activity for preventing or treating central nervous diseases and disorders (for example, ischemic central nervous disorders (e.g., cerebral infarct, cerebral bleeding, cerebral edema etc.), central nervous system injury (for example, cranial trauma, head injury, spinal injury, whiplash injury etc.), neurodegenerative diseases (for example, Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis etc.), vascular dementia (for example, multi-infarct dementia, Binswanger's disease etc.), manic-depressive psychosis, depressive disease, ~~shizophrenia~~ schizophrenia, chronic pain, trigeminal neuralgia, migraine etc.), circulatory diseases or disorders (for example, ischemic cardiac failure (for example, cardiac infarct, angina etc.), arterial sclerosis, arterial restenosis after PTCA (percutaneous transluminal coronary angioplasty), inferior urinary tract diseases or disorders (for example, dysuria, urinary incontinence) etc.), diabetic neurosis and the like. However, currently,

since sufficiently satisfactory inhibitory agents have not been found, it has been desired to develop compounds having excellent lipid peroxidation inhibitory activity, which are sufficiently satisfactory medicaments.

Please substitute the following paragraph for the fifth paragraph starting on page 10 of the specification.

Page 10, paragraph 5 (Currently Amended)

(11) the compound described in the above (10), wherein R^1 is a lower alkyl group, R^2 is a ~~halogen atom, hydroxy or a~~ lower alkyl group which may be substituted with an optionally substituted cyclic amino, a halogen atom or a hydroxy, and R^3 is hydrogen atom or an optionally substituted phenyl group,

Please substitute the following paragraph for the second paragraph on page 11 of the specification.

Page 11, paragraph 2 (Currently Amended)

(12) the compound described in the above (10), wherein R^1 is a lower alkyl group, R^2 is a ~~halogen atom, a hydroxy or a~~ lower alkyl group which may be substituted with an optionally substituted cyclic amino group, a halogen atom or a hydroxy, R^3 is hydrogen atom or an optionally substituted phenyl group, R^4 and R^5 are a lower alkyl group, and A ring is a non-aromatic 5- to 7-membered nitrogen-containing heterocyclic ring which may be further substituted with a lower alkyl group,

Please substitute the following paragraph for the third paragraph on page 11 of the specification.

Page 11, paragraph 3 (Currently Amended)

(13) the compound described in the above (10), wherein R^1 is a lower alkyl group, R^2 is a ~~halogen atom, hydroxy or a~~ lower alkyl group which may be substituted with an optionally substituted cyclic amino group, a halogen atom or a hydroxy, R^3 is hydrogen atom or an optionally substituted phenyl group, R^4 and R^5 are independently a lower alkyl group, and A ring is a non-aromatic 5-membered nitrogen-containing heterocyclic ring which may be further substituted with a lower alkyl group,

Please substitute the following paragraph for the third paragraph on page 14 of the specification.

Page 14, paragraph 3 (Currently Amended)

(32) use of Compound (I') or a prodrug thereof for manufacturing a medicament for preventing or treating restenosis after percutaneous ~~transluminal~~ transluminal coronary angioplasty, and

Please substitute the following paragraph for the second paragraph starting on page 20 of the specification.

Page 20, paragraph 2 (Currently Amended)

Examples of the "aromatic heterocyclic group" include 5- or 6-membered aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like, as well as

8- to 12-membered aromatic fused heterocyclic groups (preferably, heterocyclic rings wherein the aforementioned 5- or 6-membered aromatic monocyclic heterocyclic group is fused with a benzene ring, or heterocyclic rings wherein the same or different two heterocyclic rings of the aforementioned 5- or 6-membered aromatic monocyclic heterocyclic group are fused) such as benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, ~~cinnoilyl~~ cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, ~~buteridinyl~~ pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, ~~phenoxatiynyl~~ phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, 1,2,4,5-tetrahydro-3H-3-benzazepine-3-yl and the like.

Please substitute the following paragraph for the third paragraph on page 40 of the specification.

Page 40, paragraph 3 (Currently Amended)

Examples of the "aromatic hydrocarbon group" include monocyclic or fused polycyclic aromatic hydrocarbon groups having 6 to 14 carbon atoms. Embodiments thereof include C₆₋₁₄ aryl such as phenyl, 1-naphthyl, 2-naphthyl, anthryl and the like. Among them, C₆₋₁₀ aryl such as aryl, 1-naphthyl, 2-naphthyl and the like is preferable. Particularly preferable is ~~phenyl~~, phenyl.

Please substitute the following paragraph for the fourth paragraph starting on page 40 of the specification.

Page 40, paragraph 4 (Currently Amended)

Examples of the "aromatic heterocyclic group" include 5- to 10-membered monocyclic or its fused aromatic heterocyclic groups containing 1 or more (for example, 1 to 4) heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in addition to carbon atoms. More particularly, embodiments thereof include aromatic heterocyclic rings such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, isoquinoline, quinoline, carbazole, isothiazole, isoxazole and the like, or monovalent groups obtained by removing arbitrary hydrogen atoms from a ring formed by fusion of those rings (preferably, 5- or 6-membered monocycle) with 1 or plural (preferably, 1 or 2, more preferably 1) aromatic rings (for example, benzene ring, pyridine ring etc.). Preferable examples of the "aromatic heterocyclic group" include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 8-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzothienyl, benzofuranyl, 2-thienyl, 3-thienyl, 2-benzoxazolyl, 2-benzimidazolyl, ~~2-pyridthiazolyl~~ 2-pyridothiazolyl and the like. More preferable are 2-pyridyl, 3-pyridyl, ~~3-pyridyl~~ 3-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 2-indolyl, 3-indolyl, and the like.

Please substitute the following paragraph for the third paragraph on page 43 of the specification.

Page 43, paragraph 3 (Currently Amended)

Examples of the "optionally halogenated C₁₋₆ alkylthio" include C₁₋₆ alkylthio (for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio

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etc.) and the like optionally having 1 to 3 halogen atoms (for example, fluorine, chlorine, bromine, iodine etc.), more particularly, methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, ~~is-propylthio~~ isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio and the like.

Please substitute the following paragraph for the first paragraph on page 47 of the specification.

Page 47, paragraph 1 (Currently Amended)

When Y denotes nitrogen atom, Z_a is preferably a bond.

Please substitute the following paragraph for the seventh paragraph on page 47 of the specification.

Page 47, paragraph 7 (Currently Amended)

Examples of the "divalent aliphatic hydrocarbon group which may be via oxygen atom, nitrogen atom or sulfur atom" in the "divalent aliphatic hydrocarbon group which may have substituent(s) and which may be via oxygen atom, nitrogen atom or sulfur atom" represented by Z_b denotes ~~divalent groups optionally containing 1 or 2, preferable 1 oxygen atom, nitrogen atom or sulfur atom between carbon atoms or at its terminal, which is obtained by removing each one hydrogen atom bonding to different two carbon atoms of~~ (i) methylene or (ii) divalent groups obtained by removing each one of hydrogen atoms bonding to different two carbon atoms of saturated or unsaturated aliphatic hydrocarbon, which optionally contain 1 or 2, preferable 1 oxygen atom, nitrogen atom or sulfur atom between carbon atoms or at its terminal. Among them, groups having 1 to 8 carbon atoms are preferable.

Please substitute the following paragraph for the second paragraph starting on page 51 of the specification.

Page 51, paragraph 2 (Currently Amended)

When A ring is a non-aromatic 5-membered nitrogen-containing heterocyclic ring represented by the formula: ~~-(CH₂)_m-N(R'')-C(=O)-R'~~ -(CH₂)_m-N(R'')-C(=O)-R' (wherein R' denotes an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group, R'' denotes hydrogen atom or an optionally substituted hydrocarbon group, and M denotes an integer of 1 to 4) in the above formula (i) B ring denotes a benzene ring which has further substituent(s).

Please substitute the following paragraph for the fifth paragraph starting on page 54 of the specification.

Page 54, paragraph 5 (Currently Amended)

R² is preferably a ~~halogen atom, hydroxy or a~~ lower alkyl group (for example, C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, hexyl etc.) which may be substituted with a halogen atom or a hydroxy, or an optionally substituted cyclic amino group (the aforementioned "optionally substituted cyclic amino group", in particular, preferably D ring is 1,2,4,5-tetrahydro-3H-benzazepine, piperidine or piperazine, Y is CH, Za is a bond or a group represented by the formula NR⁹ (R⁹ is as defined above), Zb is a bond or a group represented by the formula -(CH₂)_p-M-(CH₂)_q- (symbols in the formula are as defined above), and Zc is (1) C₁₋₆ alkyl optionally substituted with 1 or 2 C₆₋₁₄ aryls, or (2) C₆₋₁₄ aryl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-indolyl, 3-indolyl or benzimidazole, each optionally having 1 to 3 substituents selected ~~form~~ from a halogen atom, C₁₋₆ alkoxy and C₁₋₆ alkyl), and the like.

Please substitute the following paragraph for the fifth paragraph starting on page 55 of the specification.

Page 55, paragraph 5 (Currently Amended)

In the above formula, preferably, R^1 is a lower alkyl group (for example, C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, hexyl etc.), R^2 is ~~a halogen atom, hydroxy, or~~ a lower alkyl group (for example, C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, hexyl etc.) optionally substituted with an optionally substituted cyclic amino group (the aforementioned "optionally substituted cyclic amino group"), halogen atom or hydroxy, R^3 is hydrogen atom or a phenyl group optionally having a substituent (C_{1-6} alkyl group such as methyl etc.), R^4 and R^5 are a lower alkyl group (preferably, C_{1-6} alkyl group such as methyl, t-butyl etc.), and A ring is a non-aromatic 5- to 7-membered nitrogen-containing heterocyclic ring (preferably a non-aromatic 5-membered nitrogen-containing heterocyclic ring) which may be further substituted with a lower alkyl group (preferably, C_{1-5} alkyl group such as methyl etc.).

Please substitute the following paragraph for the third paragraph starting on page 61 of the specification.

Page 61, paragraph 3 (Currently Amended)

Examples of the "base" include inorganic bases such as sodium hydroxide, potassium hydroxide and the like, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate and the like, aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, alkali metal hydrides such as sodium hydride, potassium hydride and the like, metal amides such as ~~sodiumamide~~ sodium amide,

~~lithiumdiisopropylamide~~ lithium diisopropylamide, ~~lithiumhexamethyldisilazide~~ lithium hexamethyldisilazide and the like, metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like. The amount of the base to be used is about 1.0 to about 5.0 mole, preferably about 1.0 to about 2.0 mole relative to 1 mole of Compound (II).

Please substitute the following paragraph for the fourth paragraph on page 70 of the specification.

Page 70, paragraph 4 (Currently Amended)

Examples of the "base" include inorganic bases such as sodium hydroxide, potassium hydroxide and the like, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate and the like, aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, alkali metal hydrides such as sodium hydride, potassium hydride and the like, metal amides such as ~~sodiumamide~~, ~~lithiumdiisopropylamide~~, ~~lithiumhexamethyldisilazide~~ sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide and the like, metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like. The amount of the base to be used is about 1.0 to about 5.0 mole, preferably about 1.0 to about 2.0 mole relative to 1 mole of Compound (IX).

Please substitute the following paragraph for the second paragraph starting on page 76 of the specification.

Page 76, paragraph 2 (Currently Amended)

Compound (XIV) is prepared by alkylating Compound (XIII). In this reaction, Compound (XII) and a corresponding alkylating agent (for example, corresponding alkyl halide, sulfonic ester of alcohol etc.) are reacted optionally in the presence of a base. The alkylating agent is used at an amount of about 1.0 to about 5.0 mole, preferably about 1.0 to about 2.0 mole relative to 1 mole of Compound (XIII). Examples of the base include inorganic bases such as sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate and the like, aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, alkali metal hydrides such as sodium hydride, potassium hydride and the like, metal amides such as ~~sodiumamide, lithiumdiisopropylamide, lithiumhexamethyldisilazide~~ sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like. The base is used at an amount of about 2.0 to about 1.0 mole, preferably about 2.0 to about 5.0 mole relative to 1 mole of Compound (XIII). This reaction is advantageously carried out by using an inert solvent. Such solvent is not particularly limited as long as the reaction proceeds. For example, solvents such as alcohols, ethers, aliphatic hydrocarbons, aromatic hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides and the like or a mixture thereof are preferable. The reaction time is usually about 30 minutes to about 48 hours, preferably about 1 hour to about 24 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 150°C.

Please substitute the following paragraph for the second paragraph starting on page 78 of the specification.

Page 78, paragraph 2 (Currently Amended)

Compound (XV) is prepared by formylating Compound (XIV). In this reaction, Compound (XIV) is reacted with dichloromethyl alkyl ethers in the presence of an acid catalyst and then hydrolyzed to obtain formyl compound. Examples of the dichloromethyl alkyl ethers include dichloromethyl methyl ether, dichloromethyl butyl ether and the like. The dichloromethyl alkyl ethers are used at an amount of about 1.0 to about 10.0 mole, preferably about 1.0 to about 5.0 mole relative to 1 mole of Compound (XIV). Examples of the acid catalyst include titanium (IV) chloride, aluminum chloride, tin (IV) chloride and the like. The acid catalyst is used usually at an amount of about 1.0 to about 10.0 mole, preferably about 1.0 to about 5.0 mole relative to 1 mole of Compound (XIV). This reaction is advantageously carried out by using an inert solvent. Such solvent is not particularly limited as long as the reaction proceeds. For example, solvents such as ethers, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, nitriles and the like or a mixture thereof are preferable. The reaction time is usually 10 minutes to 48 hours, preferably 30 minutes to 24 hours. The reaction temperature is usually -20 to 100°C, preferably 0 to 80°C. The subsequent hydrolysis is performed by mixing the reaction solution with water. Alternatively, formylation may be carried out under Vilsmeier reaction conditions. In this method, formamides are reacted in the presence of an acid catalyst and then hydrolyzed with a base to obtain the formyl compound. Examples of the formamides include methylformamide, dimethylformamide and the like. The formamides are used at an amount of about 1.0 to about 10.0 mole, preferably about 1.0 to about 5.0 mole relative to 1 mole of Compound (XIV). Examples of the acid catalyst include phosphoryl chloride, thionyl chloride and the like. The acid catalyst is used usually at an amount of about

1.0 to about 10.0 mole, preferably about 1.0 to about 5.0 mole relative to 1 mole of Compound (XIV). This reaction is advantageously carried out by using an inert solvent. Such solvent is not particularly limited as long as the reaction proceeds. For example, solvents such as amides, ethers, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, ~~nitrils~~ nitriles and the like or a mixture thereof are preferable. The reaction time is usually 10 minutes to 48 hours, preferably 30 minutes to 24 hours. The reaction temperature is usually -20 to 100°C, preferably 0 to 80°C. Subsequent hydrolysis is carried out by mixing the reaction solution with a base. Examples of the base include inorganic bases such as sodium hydroxide, potassium hydroxide, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate and the like. The amount of the base to be used is about 1.0 to about 30.0 mole, preferably about 5.0 to about 10.0 mole relative to 1 mole of Compound (XIV). Although the product may be used in the next reaction as the reaction solution itself or a crude product, it may be isolated from the reaction mixture according to a conventional method, and may be easily purified by a separating means such as recrystallization, distillation, chromatography, and the like.

Please substitute the following paragraph for the second paragraph starting on page 84 of the specification.

Page 84, paragraph 2 (Currently Amended)

Compound (XVII) is prepared by reducing Compound (XVI). Examples of a reducing agent which is used for reduction include metal hydrides such as aluminum hydride, diisobutylaluminium hydride and the like, metal hydrogen complex compounds such as lithium aluminum hydride, sodium borohydride and the like, borane complexes such as borane tetrahydrofuran complex, borane dimethyl sulfide complex and the like, alkylboranes such as

thexylborane, ~~diisiamylborane~~ disiamylborane and the like, diborane, or metals such as zinc, aluminum, tin, iron and the like, an alkali metal such as sodium, lithium and the like in liquid ammonia (Birch reduction) and the like. In addition, as a hydrogenation catalyst, catalysts such as palladium carbon, platinum oxide, Raney nickel, Raney cobalt and the like are used. The amount of the reducing agent to be used is about 1.0 to about 10 mole, preferably about 1.0 to about 3.0 mole relative to 1 mole of Compound (XVI) in the case of metal hydrides, about 1.0 to about 10 mole, preferably about 1.0 to about 3.0 mole relative to 1 mole to Compound (XVI) in the case of metal hydrogen complex compounds, about 1.0 to about 5.0 mole relative to 1 mole of Compound (XVI) in the case of borane complexes, alkylboranes or diborane, about 1.0 to about 20 equivalents, preferably about 1 to about 5 equivalents in the case of metals, about 1 to about 20 equivalents, preferably about 1 to about 5 equivalents when an alkali metal is used, catalysts such as palladium carbon, platinum oxide, Raney nickel, Raney cobalt and the like are used at an amount of about 5 to about 1000% by weight, preferably about 10 to about 300% by weight relative to Compound (XVI) in the case of hydrogenation. This reaction is advantageously carried out by using an inert solvent. Such solvent is not particularly limited as long as the reaction proceeds. For example, solvents such as alcohols, ethers, aliphatic hydrocarbons, aromatic hydrocarbons, amides, organic acids and the like or a mixture thereof are preferable. The reaction time is different depending upon a kind or an amount of a reducing agent used or the activity and amount of a catalyst and is usually about 1 hour to about 100 hours, preferably about 1 hour to about 50 hours. The reaction temperature is usually about 0 to about 120°C, preferably about 20 to about 80°C. When the hydrogenation catalyst is used, hydrogen pressure is usually about 1 to about 100 atmospheres. Although the product (XVII) may be used in the next reaction as the reaction solution itself or as a crude product, it may be isolated from the reaction mixture according to a conventional method, and may be easily

purified by a separating means such as recrystallization, distillation, chromatography and the like.

Please substitute the following paragraph for the second paragraph starting on page 86 of the specification.

Page 86, paragraph 2 (Currently Amended)

Compound (XVIII) is prepared by oxidizing Compound (XVII) with an oxidizing agent, which is subsequently treated with a base to cyclize it. As the oxidizing agent, diammonium cerium nitrate is frequently used. The oxidizing agent is used at an amount of about 1.0 to about 10 mole, preferably about 1.0 to about 3.0 mole relative to Compound (XVII). This reaction is advantageously carried out by using an inert solvent. Such solvent is not particularly limited as long as the reaction proceeds. For example, mixed solvents such as water and nitriles, alcohols, ethers, aliphatic hydrocarbons, aromatic hydrocarbons, amides and the like are **preferably** **preferable**. The reaction time is different depending upon a kind or an amount of an oxidizing agent used or the activity and amount of a catalyst and is usually about 10 minutes to about 5 hours, preferably about 30 minutes to about 1 hour. The reaction temperature is usually about -10 to about 120°C, preferably about 0 to about 60°C. Compound (XVIII) which is a cyclized product can be prepared by treating the resulting benzoquinoline with a base. Examples of the base include inorganic bases such as sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, sodium bicarbonate and the like, aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like. As a reaction solvent, the same ones as solvents used for the oxidizing reaction are used. The reaction temperature is usually about -20

to about 150°C, preferably about 0 to about 100°C. The reaction time is usually about 5 minutes to about 24 hours, preferably about 10 minutes to about 5 hours. The product (XVIII) may be isolated from the reaction mixture according to a conventional method, and may be easily purified by a separating means such as recrystallization, distillation, chromatography and the like.

Please substitute the following paragraph for the second paragraph on page 93 of the specification.

Page 93, paragraph 2 (Currently Amended)

Compound ~~(XII)~~ (XXII) is prepared by deprotecting phenylboronic acid using hydrogen peroxide, 1,3-propanediol, diethanolamine or the like. At this point, a solvent which is inert for the reaction such as benzene, toluene and the like may be used as an auxiliary solvent. The reaction time is different depending upon the amount of reagents used, a kind of the solvent or the reaction temperature and is usually about 10 minutes to about 48 hours, preferably about 5 hours to about 16 hours. Although the product may be used in the next reaction as the reaction solution itself or as a crude product, it may be isolated from the reaction mixture according to a conventional method, and may be easily purified by a separating means such as recrystallization, distillation, chromatography and the like.

Please substitute the following paragraph for the fifth paragraph on page 93 of the specification.

Page 93, paragraph 5 (Currently Amended)

Examples of the "base" include inorganic bases such as sodium hydroxide, potassium hydroxide and the like, basic salts such as sodium carbonate, potassium carbonate, cesium

carbonate, sodium bicarbonate and the like, aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, alkali metal hydrides such as sodium hydride, potassium hydride and the like, metal amides such as ~~sodiumamide,~~ ~~lithiumdiisopropylamide,~~ ~~lithiumhexamethyldisilazide~~ sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide and the like, metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like. The amount of the base to be used is about 0.8 to about 5.0 mole, preferably about 1.0 to about 2.0 mole relative to 1 mole of Compound (XXII).

Please substitute the following paragraph for the second paragraph on page 101 of the specification.

Page 101, paragraph 2 (Currently Amended)

Compound (XXXI) can be prepared by reacting Compound (XXX) and alkylchlorosulfonium ethyl acetate and, then, after reaction in the presence of a base, if necessary, heat-treating or acid-treating it to construct an oxyindole ring according to a method of Gassman et al. described in J. Am. Chem. Soc., vol.95, 6508-6509, 1973. Alkylchlorosulfonium ethyl acetate is obtained by chlorinating ethyl alkylthioacetate with chlorine, ~~sulfuryl~~ sulfuryl chloride, hypochlorite ester or the like. The chlorosulfonium ethyl acetate is used at an amount of about 0.9 to about 1.5 mole, preferably about 1.0 to about 1.2 mole relative to 1 mole of Compound (XXX). This reaction is advantageously carried out using a solvent which is inert for the reaction. Such solvent is not particularly limited as long as the reaction proceeds. Halogenated hydrocarbons and the like are preferable. The reaction time is usually about 5 minutes to about 5 hours, preferably about 30 minutes to about 2 hours. The U.S. Patent Application Serial No. 10/069,314

reaction temperature is usually about -100 to about 50°C, preferably about -80 to about 50°C. Examples of the base include aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, N,N,N',N'-tetramethyl-1,8-naphthalenediamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like. The reaction temperature is usually about -80 to about 50°C, preferably about 0 to about 20°C. As the optionally used acid, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, sulfonic acids such as methanesulfonic acid, trifluoromethanesulfonic acid, fluorosulfonic acid and the like, formic acid, acetic acid, trichloroacetic acid and the like are used. The acid is used at an amount of about 1 to about 200 mole, preferably about 1 to about 10 mole relative to 1 mole of Compound (XXX). The reaction time is usually 1 minute to about 5 hours, preferably about 30 minutes to about 2 hours. The reaction temperature is usually about -50 to about 150°C, preferably about 0 to about 50°C. Upon this, a solvent which is inert for the reaction, such as diethyl ether, dichloromethane, toluene and the like may be used as an auxiliary solvent. Alternatively, synthesis may be performed by heating in place of treatment with an acid. The reaction temperature is 50 to 250°C, preferably 50 to 150°C. The reaction temperature is 10 minutes to 48 hours, preferably 30 minutes to 5 hours. Upon this, a solvent which is inert for the reaction, such as toluene, hexane, decalin or the like may be used as an auxiliary solvent. Although the product may be used in the next reaction as a crude product, it may be isolated from the reaction mixture according to a conventional method, and may be easily purified by a separating means such as recrystallization, distillation, chromatography and the like.

Please substitute the following paragraph for the second paragraph starting on page 104 of the specification.

Page 104, paragraph 2 (Currently Amended)

Compound (XXXIII) is prepared by reducing Compound (XXXII). Examples of the reducing agent used in reduction include metal hydrides such as aluminum hydride, diisobutylaluminium hydride and the like, metal hydrogen complex compounds such as lithium aluminum hydride, sodium borohydride, Red-Al and the like, borane complexes such as borane tetrahydrofuran complex, borane dimethylsulfide complex and the like, alkylboranes such as hexylborane, ~~diethylborane~~ disiamylborane and the like, diborane and the like. The amount of the reducing agent to be used is about 0.3 to about 10 mole, preferably about 0.5 to about 3.0 mole relative to 1 mole of Compound (XXXII) in the case of metal hydrides and metal hydrogen complex compounds, about 1.0 to about 5.0 mole relative to 1 mole of Compound (XXXII) in the case of borane complexes, alkyl boranes or diborane, and about 1.0 to about 20 equivalents, preferably about 1 to about 5 equivalents in the case of metals. This reaction is advantageously carried out by using a solvent which is inert for the reaction. As such solvent, solvents such as ethers, aliphatic hydrocarbons, aromatic hydrocarbons and the like or a mixture thereof are preferable. Although the product may be used in the next reaction as a crude product after removal of a catalyst, it may be isolated from the reaction mixture according to a conventional method, and may be easily purified by a separating means such as recrystallization, distillation, chromatography and the like.

Please substitute the following paragraph for the second paragraph starting on page 107 of the specification.

Page 107, paragraph 2 (Currently Amended)

Compound (XXXVII) is prepared by reducing Compound (XXXVI). Examples of a reducing agent used in reduction includes metal hydrides such as aluminum hydride, diisobutylaluminium hydride and the like, metal hydrogen complex compounds such as lithium aluminum hydride, sodium borohydride and the like, borane complexes such as borane tetrahydrofuran complex, borane dimethyl sulfide complex and the like, alkylboranes such as hexylborane, ~~diethylborane~~ disiamylborane and the like, diborane, or metals such as zinc, aluminum, tin, iron and the like, alkali metals such as sodium, lithium and the like in liquid ammonia (Birch reduction) and the like. In addition, as a hydrogenation catalyst, catalysts such as palladium carbon, platinum oxide, Raney nickel, Raney cobalt and the like are used. The amount of the reducing agent is about 1.0 to about 10 mole, preferably about 1.0 to about 3.0 mole relative to 1 mole of Compound (XXXVI) in the case of metal hydrides, about 1.0 to about 10 mole, preferably about 1.0 to about 3.0 mole relative to 1 mole of Compound (XXXVI) in the case of metal hydrogen complex compounds, about 1.0 to about 5.0 mole relative to 1 mole of Compound (XXXVI) in the case of borane complexes, alkyl boranes or diborane, about 1.0 to about 20 equivalents, preferably about 1 to about 5 equivalents in the case of metals, about 1 to about 20 equivalents, preferably about 1 to about 5 equivalents in the case of alkali metals, and catalysts such as palladium carbon, platinum oxide, Raney nickel, Raney cobalt and the like are used at an amount of about 5 to about 1000% by weight, preferably about 10 to about 300% by weight relative to Compound (XXXVI) in the case of hydrogenation. This reaction is advantageously carried out using a solvent which is inert for the reaction. Such solvent is not particularly limited as long as the reaction proceeds. For example, solvents such as alcohols, ethers, aliphatic hydrocarbons, aromatic hydrocarbons, amides, organic acids and the like or a

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mixture thereof are preferable. Upon the use of Raney nickel and Raney cobalt catalysts, amines such as ammonia and the like may be further added in order to inhibit side reactions. The reaction time is different depending upon a kind and the amount of the reducing agent or the activity and amount of the catalyst and is usually about 1 hour to about 100 hours, preferably about 1 hour to about 50 hours. The reaction temperature is usually about 0 to about 120°C, preferably about 20 to about 80°C. When a hydrogenation catalyst is used, hydrogen pressure is usually about 1 to about 100 atmospheres. Although the product may be used in the next reaction as the reaction solution itself or as a crude product, it may be isolated from the reaction mixture according to a conventional method, and may be easily purified by a separating means such as recrystallization, distillation, chromatography and the like.

Please substitute the following paragraph for the fourth paragraph on page 116 of the specification.

Page 116, paragraph 4 (Currently Amended)

Compound (I) or (I') of the present invention exhibits the lipid peroxidation inhibitory activity based on the excellent antioxidant activity to a mammal (for example, mouse, rat, hamster, rabbit, cat, dog, cow, sheep, monkey, human being etc.) and is effective for preventing and/or treating central nervous diseases and disorders (e.g., ischemic central nervous disorders (for example, cerebral infarct, cerebral bleeding, cerebral edema etc.), central nervous system injury (for example, cranial trauma, head injury, spinal injury, whiplash injury etc.), neurodegeneration disease (for example, Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis etc.), vascular dementia (for example, multi-infarct dementia, Binswanger's disease etc.), manic-depressive psychosis, depressive disease, ~~schizophrenia~~ **schizophrenia**, chronic pain, trigeminal neuralgia, migraine etc.), circulatory

disease or disorder (for example, ischemic cardiac failure (for example, cardiac infarct, angina etc.), arterial sclerosis, arterial restenosis after PTCA (percutaneous ~~transluminal~~ transluminal coronary angioplasty), inferior urinary tract disease or disorder (for example, excretion disorder, urinary incontinence) etc.), diabetic neurosis and the like and, thus, is used as an agent for preventing or treating these diseases.

Please substitute the following paragraph for the fifth paragraph on page 119 of the specification.

Page 119, paragraph 5 (Currently Amended)

Examples of the disintegrating agent include starch, carboxymethylcellulose, potassium carboxymethylcellulose, sodium ~~cross-carmerose~~ croscarmellose, sodium carboxymethylstarch, L-hydroxypropylcellulose and the like.

Please substitute the following paragraph for the second paragraph on page 120 of the specification.

Page 120, paragraph 2 (Currently Amended)

Examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, monostearic glycerin and the like; for example, hydrophilic polymers such as ~~polybunyl~~ polyvinyl alcohol, poly(vinyl pyrrolidone), sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the ~~like,~~ like.

Please substitute the following paragraph for the third paragraph on page 131 of the specification.

Page 131, paragraph 3 (Currently Amended)

2,3-Dihydro-6,7-dimethyl-5-[(2-methyl-2-propenyl)oxy]-1H-indole-1-~~carbaldehyde~~
carbaldehyde

Please substitute the following paragraph for the fourth paragraph on page 132 of the specification.

Page 132, paragraph 4 (Currently Amended)

2,3-Dihydro-5-hydroxy-6,7-dimethyl-4-(2-methyl-2-propenyl)-1H-indole-1-~~carbaldehyde~~ **carbaldehyde**

Please substitute the following paragraph for the fourth paragraph on page 142 of the specification.

Page 142, paragraph 4 (Currently Amended)

4-Methoxy-2,3-dimethylnitrobenzene (21.1 g, 0.15 mol) was dissolved in ethanol (300 mL), and 10% palladium carbon (50% hydrate, 1.36 g) was added. The mixture was reacted at 40°C for 2 hours under the hydrogen atmosphere. After ~~cooled~~ **cooling**, the catalyst was removed, ethanol was distilled off under reduced pressure, and the residue was diluted with ethyl acetate. The dilution was washed with 5% sodium hydrosulfite, dried over sodium sulfate, and purified by small amount silica gel column chromatography (ethyl acetate, 1:1). The solvent was distilled off under reduced pressure, followed by recrystallization from hexane, to obtain 15.8 g of the title compound.

Yield 70%

¹H-NMR (CDCl₃) δ 2.10 (3H, s), 2.17 (3H, s), 2.95 (2H, br), 3.75 (3H, s), 6.53 (1H, d, J = 8.6 Hz), 6.62 (1H, d, J = 8.6 Hz)

Please substitute the following paragraph for the fourth paragraph on page 143 of the specification.

Page 143, paragraph 4 (Currently Amended)

To a solution of methyl (methylthio)acetate (40.8 mL, 317 mmol) in dichloromethane (1100 mL) was added sulfuryl chloride (26.6 mL, 331 mmol) at -78°C, and the mixture was stirred for 15 minutes. Further, a solution of 4-methoxy-2,3-dimethylaniline (41.7 g, 276 mmol) and proton sponge (62.1 g, 290 mmol) in dichloromethane (200 mL) was added dropwise over 1 hour and mixture was stirred at the same temperature for 1 hour. Triethylamine (43 mL, 380 mmol) was added, and ~~a~~ **the** temperature was gradually raised to room temperature. After ~~stirred~~ **stirring** at room temperature for 2 hours, water was added, the organic layer was washed with an aqueous saturated solution of sodium bicarbonate and saturated brine, dried over sodium sulfate, and the solvent was distilled off under reduced pressure. To the residue was added toluene (300 mL), and the mixture was stirred at reflux for 1 hour. The solvent was distilled off under reduced pressure, which was recrystallized from ethyl acetate to obtain 30.0 g of the title compound.

Yield 46%

¹H-NMR (CDCl₃) δ 2.03 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.82 (3H, s), 4.27 (1H, s), 6.82 (1H, s), 8.85 (1H, brs)

Please substitute the following paragraph for the seventh paragraph on page 144 of the specification.

Page 144, paragraph 7 (Currently Amended)

To a solution of 6,7-dimethyl-5-methoxy-1,3-dihydro-2H-indole-2-one (17.5 g, 91.5 mmol) in THF (500 mL) was added dropwise 1M-borane THF complex salt (306 mmol) at 0°C, and the mixture was stirred at 60°C ~~of~~ for 3 hours. After ~~ice-cooled~~ ice-cooling, the mixture was added dropwise to water (100 mL). THF was distilled off under reduced pressure, concentrated hydrochloric acid (100 mL) was added, and the mixture was stirred under reflux for 2 hours. After ~~neutralized~~ neutralizing with 12N sodium hydroxide under ice-cooling, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, and purified by small amount silica gel column chromatography (ethyl acetate). The solvent was distilled off under reduced pressure, followed by recrystallization from hexane, to obtain 8.18 g of the title compound.

Yield 66%

mp. 54-56°C

¹H-NMR (CDCl₃) δ 2.07 (3H, s), 2.12 (3H, s), 3.03 (2H, t, J = 8.3 Hz), 3.53 (2H, t, J = 8.3 Hz), 3.76 (3H, s), 6.65 (1H, s).

Please substitute the following paragraph for the fourth paragraph on page 147 of the specification.

Page 147, paragraph 4 (Currently Amended)

To a solution of 6,7-dimethyl-5-methoxy-1,2-dihydro-1H-indole (2.0 g, 11.3 mmol) in THF (20 mL) were added triethylamine (2.4 mL, 17.2 mmol) and di-tert-butyl dicarbonate (2.68 g, 12.3 mmol) at 0°C. After ~~stirred~~ stirring at room temperature for 1 hour, the solvent was

distilled off under reduced pressure, followed by recrystallization from hexane to obtain 2.27 g of the title compound.

Yield 73%

mp. 124-128°C

¹H-NMR (CDCl₃) δ 1.51 (9H, s), 2.13 (3H, s), 2.16 (3H, s), 2.93 (2H, t, J = 7.3 Hz), 3.78 (3H, s), 4.07 (2H, t, J = 7.3 Hz), 6.64 (1H, s)

Please substitute the following paragraph for the third paragraph on page 153 of the specification.

Page 153, paragraph 3 (Currently Amended)

1,6,7,8-Tetrahydro-2-(~~iodomethyl~~ iodomethyl)-2,4,5-trimethyl-2H-furo[3,2-e]indole

Please substitute the following paragraph for the fourth paragraph on page 155 of the specification.

Page 155, paragraph 4 (Currently Amended)

To a solution of 1,6,7,8-tetrahydro-2-(iodomethyl)-2,4,5,7,7-pentamethyl-2H-furo[3,2-e]indole-6-carbaldehyde (1.93 g, 4.83 mmol) in methanol (10 mL) was added concentrated hydrochloric acid (3 mL), and the mixture was heated to reflux for 3 hours under the nitrogen atmosphere. The reaction mixture was added dropwise to a mixture of sodium bicarbonate (3.7 g, 44 mmol) in water-ethyl acetate to neutralize, which was extracted with ethyl acetate two times. The combined organic layers were washed with water and saturated brine, dried over magnesium sulfate, ~~filtered.~~ filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 10:1) to obtain 1.56 g of the title compound.

Yield 87%

Amorphous

$^1\text{H-NMR}$ (CDCl_3) δ 1.34 (6H, s), 1.64 (3H, s), 1.70-2.70 (1H, br), 2.00 (3H, s), 2.07 (3H, s), 2.75 (2H, s), 2.90 (1H, d, $J = 15.8$ Hz), 3.16 (1H, d, $J = 15.8$ Hz), 3.41 (2H, s)